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Psoriatic Arthritis Mutilans: Characteristics and Natural Radiographic History

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ABSTRACT

Objectives: To (1) compare clinical characteristics of psoriatic arthritis (PsA) patients with PsA mutilans (PAM) and without PAM; (2) determine the rate of PAM radiographic progression.

Methods: A retrospective cohort study was conducted of all PsA patients attending a teaching hospital. The most recent hand and feet radiographs were screened for PAM. Serial radiographs (earliest to most recent) were quantitatively scored for osteolysis, erosion, joint space narrowing, and osteoproliferation.

Results: 36/610 (5.9%) PsA cases had PAM. PAM cases were younger at diagnosis of PsA than non-PAM cases (p=0.04), had more prevalent psoriatic nail dystrophy (OR 5.43; p<0.001), and worse HAQ (1.25 *vs*. 0.62; p<0.04). Radiographic axial disease (OR 2.31;adjusted p=0.03), especially radiographic sacroiliitis (OR 2.99; p=0.01) were more prevalent in PAM. PAM were more likely than non-PAM cases to have used a DMARD (OR 16.36; p<0.001). 29/33 PAM cases had initiated a synthetic DMARD, and 4/13 had initiated anti-TNF, prior to first demonstration of PAM.

A median five radiographs were scored for each PAM case (IQR 3-7). PAM progressed from monoarticular (60%) to polyarticular (80%) involvement. Osteolysis was initially rapid and progressive in the hands and feet, tapering later during disease course. Nail dystrophy predicted more severe osteolysis (p=0.03).

Conclusion: Compared to non-PAM cases, PAM cases have earlier age at PsA diagnosis, poorer function, more prevalent nail dystrophy and radiographic axial disease / sacroiliitis. The rate of osteolysis is higher in earlier disease, and more severe in those with nail dystrophy. DMARDs and anti-TNF appear not to prevent PAM occurrence.

MeSH terms

Arthritis, Psoriatic; History, Natural; Nail, Malformed; Radiographs; Tumor Necrosis Factor-alpha

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease of the musculoskeletal system, that can also affect extra-articular structures. Five patterns of PsA were described in 1973 by Moll *et al.*: asymmetric oligoarthritis, symmetric polyarthritis, distal interphalangeal joint-predominant arthritis, spondylitis, and arthritis mutilans (1). The most extreme, albeit rarest form of PsA is psoriatic arthritis mutilans (PAM).

Arthritis mutilans is a condition characterised by severe destruction of the joint and adjacent bone through erosion and subsequent osteolysis. As a result of soft-tissue laxity and loss of bone stock, fingers and toes can shorten, giving rise to thick transverse folds of skin, and digits that can be elongated with traction. Two such cases were first described in 1913 by Marie *et al.*, who compared the phenomena with the telescopic action of an opera glass (*la main en lorgnette*) (2). Earlier in 1888, Bourdillon first reported a resorptive arthropathy associated with psoriasis (3). Arthritis mutilans can occur in association with several diseases, including psoriatic arthritis (PAM) (1), rheumatoid arthritis (4, 5), chronic reactive arthritis, juvenile chronic arthritis and mixed connective tissue disease (6). Its pathogenesis is unknown.

Research of PAM has been impeded by the rarity of the subphenotype, and the lack of an agreed clinical or radiographic definition. Estimates of the prevalence of PAM in PsA cohorts range from 0.6 to 21% (1, 7-11), but are likely to be closer to 5% as was originally described by Moll and Wright (1) and subsequently by others (9-11). A recent population-based study estimated the prevalence of PAM in the adult Nordic population to be 3.69 per million inhabitants, and with similar sex distribution (12). Studies to date have been cross-sectional, with no longitudinal data. Recent reports are mostly case series (13-15), with a few studies of between 6 to 24 cases each (9, 10, 16-19), and only one large study of 59 cases (12). The majority of studies simply note the occurrence of PAM in a general PsA cohort. To our knowledge, the natural clinical and / or radiographic history of PAM has never been described.

Our study objectives were to: (1) compare the clinical characteristics of PsA patients with PAM and without PAM (non-PAM); (2) determine the rate of PAM radiographic progression.

MATERIALS & METHODS

A retrospective cohort study was conducted of all PsA patients attending a dedicated PsA outpatient clinic at a secondary-care teaching hospital. Patients attending clinic had plain radiographs of hands and feet performed at intervals determined by usual clinical care; and dated from 1974 to 1 December 2013 (census). The case notes and clinical data collection proforma (from other prospective longitudinal studies at our institution) of PsA cases provided clinical data including: sex, date of birth, age at psoriasis symptom onset, age at psoriasis diagnosis, age at PsA arthritis symptom onset, age at PsA diagnosis, smoking history (never, ever, current), alcohol consumption (never, ever, current), nail dystrophy at any time during disease course, most recent Stanford Health Assessment Questionnaire Disability Index (HAQ) (20), anti-cyclical citrullinated peptide antibody serology, synthetic disease modifying anti-rheumatic drug (DMARD) use (agent, date of initiation, date of cessation), biological therapy use in particular anti-tumour necrosis factor-alpha (anti-TNF) (agent, number of biologicals used, date of initiation, date of cessation), and corticosteroid use (in oral, intramuscular or intravenous form).

Peripheral radiographic scoring methods

As no existing plain radiographic score for PsA captures the various radiographic features of PAM, components of existing radiographic tools were used. Plain radiographs of hands and feet were quantitatively scored for osteolysis, erosion (using the PsA-modified Sharp score; mSS (21, 22)), joint space narrowing (mSS), osteoproliferation (PsA Ratingen Score; PARS (23)), periostitis (mSS), tuft resorption (mSS), and osteopaenia using the PsA-modified Steinbrocker score (24). A new domain to score osteolysis was devised to aid the detection of PAM and capture progression; with a range of 0 to 12, and based upon lysis of bone from the articular surface of the epiphysis, through the metaphysis, to the diaphysis (*Figure 1*).

Reading strategy and reliability exercise

Standard digital antero-posterior radiographs of the hands and feet were viewed and scored using the hospital's Picture Archiving and Communication System (PACS). Historical hard-film plain radiographs, preceding the advent of PACS in our institution (February 2007), were digitised to HiPAX Image Viewer for scoring. All images were read on the same viewing monitor, preserved at the original 1:1 ratio. All radiographs included a 'phantom phalanx' as a reference for normal bone mineral density.

The two readers (DJ, WT) underwent pre-study training in the precise definitions of radiographic findings of PsA (25), practice, supervision and discussion with an experienced Consultant musculoskeletal radiologist (GR). To determine inter-rater reliability, ten random pairs of hand and feet radiographs were scored by both the readers, in random order.

Identification of PAM cases

In keeping with previous publications on PAM (8, 16, 17), plain radiographic PAM was defined as osteolysis affecting ≥50% of the visualised articular surface on both sides of the joint. A large erosion qualified as osteolysis once the epiphyseal plate was encroached. PAM was therefore only called once the osteolysis score in an individual joint was ≥4 units.

The most recent plain radiographs of hands and feet were evaluated for PAM (DJ). Group consensus (DJ, WT, NM, GR) was sought for uncertain cases. All available radiographs of PAM cases (earliest to most recent) were then randomised and scored by the two readers (DJ, WT).

Axial radiographic scoring methods

All cases had their most recent axial plain radiographs (cervical spine, lumbar spine, and sacroiliac joints, as available) scored for evidence of radiographic spondylitis and / or sacroiliitis by one reader (DJ) following education and practice with GR. In keeping with previous publications (26, 27), radiographic axial disease was defined as: the presence of New York criteria unilateral grade ≥3, or bilateral grade ≥2 sacroiliitis on AP pelvic radiograph; and / or ≥1 marginal / paramarginal syndesmophyte(s) of the cervical, or lumbar spine.

Statistical analysis

Data were analysed using 'R' (28). Inter-rater reliability testing was performed using intra-class correlation coefficients (ICCs).

For univariate analyses continuity-corrected Chi-squared tests were used to test for differences between categorical variables, and independent t-tests or Mann-Whitney U-tests used for normally or non-normally distributed continuous variables, respectively. Unadjusted odds ratios (OR), associated 95% confidence intervals (95% CI), and p-values using an alpha-level of 0.05 were calculated.

Multivariate analysis was performed to compare the prevalence of axial radiographic disease in PAM and non-PAM, using a logistic regression with adjustment for sex and age at most recent pelvis radiograph. Multivariate analysis was performed to compare HAQ scores in PAM and non-PAM, using a zero-inflated Poisson regression (29) with adjustment for sex and age at HAQ assessment.

Patterns and rates of deterioration of individual joints over time were examined for all patients. Initial analysis consisted of plotting the data together with locally-weighted polynomial regression smoothers (lowess) (30). Formal modelling of the changes in scores over time was performed using generalised additive mixed models (GAMM) (31), using penalised splines to assess the complexity of the model required for each joint and allowing a random effect for each patient. For each joint, the required complexity was expressed as the effective degrees of freedom (EDF). An EDF of one signifies a linear change in scores over time, *i.e.* a constant rate of deterioration from date of diagnosis, with larger values indicating that rates of deterioration over time are more complex.

Ethical considerations

Ethical approval for the study was given by the Local Regional Ethics Committee and informed written consent obtained from participants.

RESULTS

610 PsA cases fulfilling classification criteria for psoriatic arthritis (CASPAR) (32, 33) were screened for the presence or absence of plain radiographic PAM. 36/610 (5.9%) had PAM, with 35/36 having serial radiographs. 483/610 had no evidence of PAM. 91/610 either had no radiographs of hands and feet, or only one of the two sites imaged, and therefore although unlikely, PAM could not be excluded.

Inter-rater reliability of plain radiographic scoring

The inter-rater reliability of peripheral plain radiographic scoring was very high: intra-class correlation (ICC) 0.99 (95% CI 0.98 – 1.00) for osteolysis; ICC 0.95 (95% CI 0.91 – 0.99) for erosion; ICC 0.97 (95% CI 0.95 – 0.99) for osteoproliferation; and ICC 0.90 (95% CI 0.84 – 0.93) for osteopaenia.

Clinical characteristics of PAM and non-PAM cases

The proportion of females in the PAM and non-PAM cohorts were similar (52.78 *vs*. 47.20%, respectively; p=0.52). PAM cases were younger at PsA diagnosis than non-PAM cases (median age 33.00 *vs*. 40.00 years; p=0.04), but no different in terms of age at PsA arthritis symptom onset (p=0.119), psoriasis symptom onset (p=0.86), psoriasis diagnosis (p=0.79), or age at census (p=0.05) (*Table 1*).

Psoriatic nail dystrophy was far more prevalent in PAM cases than non-PAM cases (OR 5.43; 95% CI 2.21 – 13.30; p<0.001) (*Table 2*).

Physical function, as measured by the total HAQ was more impaired in PAM cases compared to non-PAM cases on univariate analyses (median HAQ 1.25 *vs*. 0.63; p=0.04) (*Table 1*). Using zero-inflated Poisson regression, the adjusted RR was 1.12 (95% CI 0.86 -1.45; adjusted p=0.41). Differences in subdomains of the HAQ between the PAM and non-PAM cases were clinically significant, and approached statistical significance for the HAQ-reach domain (RR 1.34; p=0.05) and the HAQ-activity domain (RR 1.50; p=0.09), with differences in other subdomains being statistically non-significant.

For the patients in whom ACPA serology was available, no difference was demonstrated in ACPA-positivity in PAM (0/16) compared to non-PAM cases (8/226; p=0.44) (*Table 2*).

PAM cases were more likely to have radiographic axial disease than non-PAM cases (adjusted OR 2.31; 95% CI 1.07 – 4.97; adjusted p=0.03) (*Table 2*). PAM cases were more likely to have radiographic sacroiliitis than non-PAM cases

(adjusted OR 2.99; 95% CI 1.33 – 6.73; adjusted p=0.01). When sacroiliitis was present in PAM cases it tended to be bilateral (9/11; 81.82%) and of grade ≥3 (11/11; 100%) (*Table 2*). PAM cases were no more likely to have radiographic spondylitis than non-PAM cases (adjusted OR 1.46; 95% CI 0.65 – 3.28; adjusted p=0.36). When spondylitis was present in PAM cases it affected both the cervical (6/27; 22.22%) and lumbar spine (5/24; 20.83%).

During the course of disease, PAM cases were more likely than non-PAM cases to have used a synthetic DMARD (OR 16.36; 95% CI 3.88 – 68.96; p<0.001); including methotrexate (p<0.001), sulfasalazine (p<0.001) and leflunomide (p<0.001) (*Table 2*). Of particular note, 29/33 (87.88%) of PAM cases had initiated a DMARD before PAM was first observed radiographically (a median of six years before), implying that DMARDs do not prevent the onset of PAM.

PAM cases were no more likely than non-PAM cases to have used an anti-TNF agent (OR 1.25; 95% CI 0.62 – 2.54; p=0.53) (*Table 2*). 4/13 PAM cases had initiated an anti-TNF before the onset of radiographic PAM (5.67, 3.89, 3.72, and 1.08 years beforehand). 6/13 PAM cases initiated an anti-TNF agent after PAM onset. 3/13 cases already had PAM at their earliest radiograph.

15/36 (41.67%) PAM cases had used corticosteroids during the course of their disease in oral, intramuscular or intravenous form (*Table 2*).

Radiographic characteristics of PAM cases

The median number of films (pairs of hands and feet) scored per patient was 5 (IQR 3 – 7) (*Table 1*). The median interval from baseline to most recent film (*i.e.* duration of radiographic follow-up) was 10.87 (IQR 5.48 – 16.51) years. The median age of PAM cases at the earliest film was 47.37 (IQR 37.45 – 61.71) years, and at the most recent film was 64.54 (IQR 49.71 – 70.37) years (*Table 1*).

Whilst radiographic PAM was evident in the earliest film in 13/35 (37.14%) cases, the majority of cases (22/35; 62.86%) developed it during the course of their follow-up (*Table 3).* In the 22 cases where PAM developed during the course of follow-up, the time from diagnosis of PsA to onset of radiographic PAM was a median of 12.50 (IQR 6.00 - 18.00) years, at a median age of 49.70 (IQR 42.92 – 68.21) years (*Table 1*).

PAM was most commonly monoarticular (21/35; 60%) when first demonstrated, but progressed to being polyarticular at the most recent film (28/35; 80%) (*Table 3*). At the most recent film, the most frequently affected joint was the big toe interphalangeal joint (IPJ1) (8.81%), followed in equal frequency (6.92%) by the thumb metacarpophalangeal joint

(MCPJ1), index finger distal interphalangeal joint (DIPJ2), little finger proximal interphalangeal joint (PIPJ5), and feet metatarsophalangeal joints 2 to 5 (MTPJ2-5) (*Figure 2*).

Of note, 12/35 (34.29%) PAM cases had concurrent evidence of joint osteolysis and ankylosis within the same hand or foot (*Table 3*). 2/35 PAM cases had proceeded to having surgery on the joint affected by PAM; due to impaired hand function in one case, and pain in the other case (*Table 3*).

Radiographic progression of PAM

35/36 PAM cases had serial radiographs available for scoring. For hands and feet combined, at the most recent film the median osteolysis score was 2.00 (IQR 0.00 – 15.00) units, erosion score 9.00 (IQR 0.00 – 26.00) units, joint space narrowing score 14.00 (IQR 0.00 – 31.00) units, osteoproliferation score 3.00 (IQR 0.00 – 6.00) units, and osteopaenia score 0.00 (IQR 0.00 – 2.00) units.

A significant change in osteolysis score over time was observed for all joints ($p<0.008$). After allowing for patient differences in a random effects model, there was a strong indication that different joints had different patterns of deterioration over time ($p<0.001$).

Figure 3. shows curves from the generalised additive mixed model, including data from all 159 joints affected by PAM. The best fit regression curve, 95% confidence interval bands, and the effective degrees of freedom (EDF) for each curve are shown for the hands and feet joints separately. In the feet, there is an initial high rate of osteolysis, followed by a tapering rate, and eventually little further progression of osteolysis (EDF=3.1). However, in the hands the curve is more complex (EDF=4.3) with an initially high increase in osteolysis, followed by a tapering in the rate. For some patients there was indication of a second surge of osteolysis in some joints later during disease course, adjusted for the time since diagnosis.

PAM cases with a history of psoriatic nail dystrophy (30/36) had significantly higher overall osteolysis scores in topographically related joints (DIPJ / PIPJ / IPJ) of the hands, than those without nail dystrophy (6/36) (mean scores; 3.0 with nail dystrophy, 1.3 without nail dystrophy; $p= 0.03$).

DISCUSSION

We have taken advantage of a well-characterised cohort of PsA patients followed longitudinally in a single centre to compare the clinical characteristics of PAM and non-PAM cases, and investigate the natural radiographic history of PAM. To our knowledge, this is the largest sample of PAM cases with a detailed description of plain radiographic characteristics, and the first study to report on radiographic progression.

A previous study by our group showed that nail dystrophy is more common in PsA patients with DIP joint disease, and is significantly associated with adjacent DIP joint disease (33). Here we demonstrate that psoriatic nail dystrophy is a clinical biomarker of both PAM occurence, and of having more severe osteolysis in topographically adjacent joints (hand DIP, PIP and IP joints). This has not previously been reported. Furthermore, PAM was most commonly seen in the weight-bearing joints of the feet (MTPJ 2-5, IPJ1) and hand joints involved in power / precision grip (DIPJ2, MCPJ1). Little is known about the pathogenesis or trigger for PAM. The concept of altered biomechanical loads or stress on the synovial-entheseal complex being involved in the pathogenesis of SpA, as proposed by McGonagle *et al.* (34, 35), is supported by our current findings in PAM.

There has been debate as to whether involvement of a single joint is sufficient for a case to be defined as PAM (36). Our data indicates that 7/35 (20%) have monoarticular PAM, even after several years of follow-up. Review of these seven cases in our outpatient clinic demonstrated clinical evidence of PAM, with shortened telescopic digits. We therefore propose that PAM can be monoarticular, although it is more frequently polyarticular and the notion is supported by data from other studies (1, 12, 13, 18).

Several of our results corroborate those of the Classification of Psoriatic Arthritis (CASPAR) dataset (18), which showed that PAM cases are usually polyarticular, of long disease duration, and are more prone to spinal involvement compared to their non-PAM counterparts. In our cohort there was a higher prevalence of sacroiliitis, that tended to be more severe than in non-PAM cases, and some increase in other features of spondylitis. However, we did not replicate the CASPAR findings of more frequent ACPA-positivity (albeit of low titre) in PAM compared with non-PAM cases. Joint surgery rates in our cohort of PAM cases were far lower than the 48% reported by Helliwell *et al.* (18).

A further intriguing issue is the nature of the relationship between osteolysis and ankylosis. In our dataset, 12/35 (34.29%) cases had concurrent osteolysis and ankylosis in the same hand or foot. Occasionally, osteolysis progressed

to joint ankylosis in the same joint, but more commonly we saw joint space narrowing progressing to ankylosis, suggesting that there are two separate pathogenic processes although both may occur in the same patient.

None of our PAM cases had improvement of osteolysis, erosion or osteoproliferation scores. Joint space narrowing, osteopaenia and periostitis scores fluctuated, with both regression and progression. There are emerging reports in the literature of improvement in erosion (37, 38) and joint-space narrowing (38) scores following anti-TNF use, implying filling-in or 'healing' of previous structural damage. However, a paper reporting the follow-up of three PAM cases treated with etanercept, demonstrated no improvement in deformities resulting from several years of progressive disease (14). Furthermore, our data suggests that neither synthetic DMARDs nor anti-TNF prevent the onset of radiographic PAM. Our findings need to be interpreted with caution in a retrospective study where the radiographs were not taken at fixed time intervals, hence sensitivity to detect PAM onset is reduced, and the doses of some agents such as methotrexate were lower than those used nowadays.

The sequence of pathological events leading to the frank osteolysis of PAM is of much interest. Magnetic resonance imaging has demonstrated higher bone proliferation and oedema scores in PAM compared with non-PAM cases, and has therefore been proposed as a potential radiological biomarker of progressing to PAM (16). In our study we did not see osteopaenia or periostitis preceding the onset of erosions or osteolysis. Nor did we overtly see progressive erosions prior to the onset of osteolysis. However, we acknowledge that the varied time interval between radiographs may have reduced our sensitivity to track such changes. In our general observations we noted progressive joint space narrowing prior to the onset of osteolysis.

We acknowledge that our study has limitations. Whilst it appears that 36/519 (6.94%) of our cohort suffer PAM, we are aware that 91/610 PsA cases had insufficient or no radiographs to assess the presence or absence of PAM. The lack of radiographs may imply minimal disease activity at these sites, or may be due to non-clinical factors. Assuming that all 91 were non-PAM cases, the prevalence of PAM in our cohort falls to 36/610 (5.90%). However, both estimates are within the range of prevalence described by other authors (1, 7-11). Secondly, since the interval between films was determined by clinical need, rather than predefined intervals, we are unable to determine the incidence of PAM onset. Since PAM was evident in the earliest available radiograph in 13/35 (37.14%) of cases, the initial rate of radiographic progression could not be determined in this subgroup of patients.

To conclude, PAM is a rare but severely destructive subphenotype of PsA. Further research is need to investigate the pathogenesis of PAM, the chronology of pathological events, genetic and / or serum-soluble biomarkers of PAM, and whether anti-TNF or anti-resorptive agents may offer therapeutic efficacy.

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